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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/704,272	11/01/2000	Alan D. Attie	960296.96668	1921

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/704,272	ATTIE ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/13/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *4,7-10 and 12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,11 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 14 August 2003 has been entered. Claim 5 has been amended. Claim 22 has been added and reads on the elected invention. Claims 4, 7-10 and 12-21 were withdrawn by the examiner, and have not been cancelled. Claims 1-3, 5, 6, 11 and 22 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

URL's

The objection to the disclosure for containing browser-executable code, as set forth in the previous Office action (11 February 2003), is *withdrawn* in view of the amendment which removed all URL's from the Specification (14 August 2003).

35 USC § 112, second paragraph-indefiniteness.

The rejection of Claim 5 under 35 U.S.C. 112, second paragraph, as set forth in the previous Office Action (11 February 2003) is *withdrawn* in view of the amendment which added "direct drug inhibition" to claim 5 (14 August 2003), thus further limiting the claimed subject matter from independent Claim 3.

35 USC § 112, first paragraph-written description

The rejection of Claims 1-3, 5, 6 and 11 under 35 U.S.C. 112, first paragraph, as set forth in the previous Office Action (page 6 and 7, 11 February 2003) is *withdrawn* in view of the amendment which added a "sulfonylurea compound" to claim 22 (14 August 2003), thus describing the class of drugs used by the Applicant to inhibit the ABC1 transporter in cells.

Maintained Objections and/or Rejections

35 USC § 112, first paragraph - lack of enablement

Claims 1-3, 5, 6, 11, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein cholesterol uptake in the gut is inhibited by administering an ABC1 transporter inhibitor. The reasons for this rejection under *35 U.S.C. § 112*, first paragraph, are set forth at pages 4-5 of the previous Office Action (11 February 2003).

Claims 1-3, 5, 6, 11, 21 and 22 read on a method of inhibiting cholesterol uptake in the gut of a human or animal, by administering an inhibitor of ABC1. Dependent claims recite sulfonylurea compounds as ABC inhibitors and agents given orally.

The specification discloses the *WHAM* mutation in chickens, in which a single nucleotide substitution results in an amino acid change at residue 89 of a chicken ABC transporter. The specification documents the phenotypes of WHAM chickens as to pigmentation, phospholipid disposition and cholesterol transport (Specification pp. 25-27). *WHAM* chickens appear to share similarities to humans with Tangier's disease, such as retention of cholesterol esters in skin and connective tissues (Lawn, et al, 1999, J. Clinical Investigation, 104: 25-31). WHAM chickens and humans with Tangier's disease have reduced abilities for "reverse" cholesterol transport; this means that the pathways leading to excretion of excess cholesterol are severely compromised. In addition, concentrations of high-density cholesterol carrier proteins ("HDL" in humans) in homozygous recessive individuals are 1-5% of the normal or wild-type. These defects in cholesterol processing result in severe neuropathies, premature atherosclerosis, and early death (Remaley, et al, 1999, Proc. Natl. Acad. Sci., 96(22): 12685-12690; Asztalos, et al, 2001, Atherosclerosis, 156: 217-225).

Applicants argue (page 4, 18 August 2003):

"the fact that the human condition known as Tangier's disease and the mutation in the chickens result from a mutation in the same protein is inescapable evidence that the activity of that protein is responsible for the unique physiological conditions shared [by] [the] Tangier's patients and the chickens. That physiological condition includes reduced uptake of cholesterol from the intestines. This is compelling evidence that a reduction in ABC1 activity in the intestines will result in decreased absorption of cholesterol from the intestines. The Examiner has provided no reason whatsoever to question whether this result would be obtained."

The Applicants further remark (page 5, 18 August 2003):

"Note that this is all that Claim 1 requires. Claim 1 is a method for inhibiting cholesterol uptake in the gut. It is now known, without dispute, that ABC1 is responsible for, at least in part, cholesterol uptake in the gut. It is also known that there are demonstrated inhibitors of ABC1 activity, notably the sulfonylurea drugs. Since the

activity desired is inhibition in the gut, and delivery to the gut may be obtained by oral ingestion, there is no lack of enablement related to delivery of the compound to the active site where inhibition is desired. The Examiner has provided no reason, other than a general sense of uncertainty in the world, why this would not occur. As such a rejection of these claims for lack of enablement is improper."

Applicant's arguments filed 18 August 2003 have been fully considered but are not deemed persuasive for the following reasons:

The claims read on a method of inhibiting cholesterol uptake in the gut of an individual or animal. However, there is no enabling discussion or working examples disclosed in the instant application as to how to practice the method of inhibiting cholesterol uptake in the gut of an animal or human. This is because, as shown in WHAM chickens and in humans with Tangier's disease, ABC1 is responsible for both uptake of cholesterol from the diet, and *excretion* of cholesterol - so called "reverse" transport (see Remaley, et al, page 12685) whereby cholesterol is transported back to the liver for excretion. In fact, the net effect of inhibiting ABC1 would not be to inhibit cholesterol uptake (e.g., from the diet), but rather to inhibit overall net cholesterol excretion. Humans with Tangier's disease have very low HDL levels, and high concentrations of cholesterol in tissues, including blood vessels. Application of ABC1 inhibitors, such as sulfonylurea drugs, would result in a condition similar to Tangier's disease: a net decrease in cholesterol excretion and pathological levels of cholesterol esters in sensitive tissues such as nerves, glands and blood vessels.

Proper analysis of the Wands factors was provided in the previous Office Action (11 February 2003). Due to the large quantity of experimentation required to: determine

how to administer, control side effects, and use an ABC inhibitor to inhibit net cholesterol transport across the gut, the lack of direction or guidance in the specification regarding the same, the lack of working examples that use a sulfonylurea *in-vivo*, the state of the art showing the complexities of cholesterol transport regulation, and the breadth of the claims which embrace in-vivo inhibition of net cholesterol transport -- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW
12/27/03

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER